REMARKS

Claims 1, 3, 10-12, 17-20, 23-27, 34-38, 42-44, 47, 49-52, 54-56, 58 and 59 are pending. The Examiner has withdrawn claims 2, 4-8, 13-16, 21, 22, 28, 29, 31, 40, 41, 45, 46, 48 from consideration as being drawn to a non-elected species and these non-elected claims are hereby canceled without prejudice with Applicant reserving the right to pursue the subject matter covered therewith in future divisional applications.

Claims 17 and 37 have been amended to more particularly point out and distinctly claim the subject matter which the applicant regards as her invention. No new matter has been added. Applicants respectfully request entry of this amendment.

Claim of Priority to U.S. 09/204,254, now U.S. Patent No. 6,369,039

Examiner has acknowledged Applicant's claim to the benefit of the prior-filed copending nonprovisional application U.S. Ser. No. 09/204,254, filed December 3, 1998 now U.S. Patent No. 6,369,039 B1.

The Examiner has entered Applicant's claim of priority to U.S. 09/204,254 now U.S. Patent No. 6,369,039 (the '039 patent). However, the Examiner opines that Applicant has not complied with the requirements of 23 U.S.C. § 120 because the claims of the subject application are allegedly not supported in the '039 patent commensurate with 35 U.S.C. § 112, first paragraph. Applicants respectfully disagree.

The paragraph at col. 4, line 64 to col. 5, 48 teaches which therapeutic agents can be in the coating. The paragraph lists various polynucleotides that can be present in the coating (col. 4, line 67 to col. 5, line 4) as well as "vascular cell growth promoters such as growth factors" (col. 5, lines 31-32). Growth factors are proteins so they are "non-genetic" and if they promote vascular growth they are "angiogenic agents." Col. 5, line 44 states that the preceding therapeutic agents can be used in combination. So that provides a combination of polynucleotides and "non-genetic" angiogenic agents in the coating. The polynucleotides can code for therapeutic polypeptides (col. 5, lines 55-56) and the polypeptides so encoded can be angiogenic factors (col. 5, lines 62-65). As such, the '039 patent provides written description for the claims at issue and they should be afforded the benefit of the earlier filing date.

In view of Applicants' arguments and amendments, the Examiner has withdrawn the previous grounds for rejection under 35 U.S.C. §§ 102 and 103 and asserted the rejections below. Applicant respectfully traverses as follows.

Rejection of Claims 1, 3, 10-12, 17-20, 22-27, 30, 34-38, 42-44, 47, 49-52, 54-56, 58, 59 under 35 U.S.C. § 112, First Paragraph - Written Description

The Examiner has rejected claim 1, 3, 10-12, 17-20, 22-27, 30, 34-38, 42-44, 47, 49-52, 54-56, 58, 59 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor had possession of the claimed invention at the time the application was filed.

The Examiner states that the amendment of claims 1 and 26 in the response pursuant to 37 C.F.R. § 1.111 filed March 17, 2003 adds new matter into the subject application. Applicant respectfully disagrees.

The Examiner contends that the original specification does not disclose a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; and a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent.

Specifically, the Examiner feels that even though the specification sets forth a list of products that the vector and carrier can carry, there is "nothing in the specification that would lead one to the particular combination set forth in the amended claims."
(Final Office Action mailed June 4, 2003, page 4, lines 10-11). MPEP 2163.05 II states:

> The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 39 USPQ2d 1895 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not **"reasonably lead"** those skilled in the art to any particular species.) [emphasis added]

Applicant asserts that the clear description in the subject specification goes well beyond one that would merely "reasonably lead" the skilled artisan to the claimed invention, as was found lacking in *Fujikawa, supra*. Applicant respectfully asserts that one of skill in the art would not only reasonably be lead to but instantly appreciate the claimed invention when reading the specification, specifically, the preferred embodiment and Example 7.

As indicated on pages 22-23:

> A preferred embodiment of this invention is to provide treatment of vascular thrombosis and angioplasty restenosis, particularly coronary vascular thrombosis, and angioplasty restenosis, thereby to decrease incidence of vessel rethrombosis and restenosis, unstable angina myocardial infarction

> and sudden death. The medical device and method of this invention can be used to treat patients having severe complications resulting from thrombus. Specific examples include patients with acute myocardial infarction (AMI) and patients that have failed PTCA (percutaneous transluminal coronary angioplasty) and have abrupt thrombotic closure of the targeted artery.

From this passage, one of ordinary skill in the art would readily recognize that the mechanism by which the applicants intend the preferred embodiment of the invention operates is to increase blood flow and thereby oxygen delivery to tissues, particularly to tissues sensitive disruptions in cardiovascular perfusion, i.e. myocardium, etc. The person of skill in the art would further recognize that the incidences of such disturbances in blood flow to such tissues could be reduced if through a local increase of blood flow through the development and expansion of vessels in an area of potential stenosis of thrombotic blockage. The localized development and expansion of blood vessels is referred to as angiogenesis.

Furthermore, in Example 7 on page 29, the specification discloses a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent and wherein the second therapeutic agent is also an angiogenic agent. The example discloses a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes VEGF protein, as a delayed expression vector; and a second therapeutic agent comprising a second polynucleotide wherein the second polynucleotide encodes FAS Ligand protein und the control of an SV40 early expression promoter.

The specification indicates that VEGF protein is a "promoter of endothelialization" (Example 7, page 29, line 3), i.e., angiogenesis. VEGF protein is known to play a critical and central role in angiogenesis. FAS Ligand is also thought to have a role in promoting angiogenesis. See Biancone et al., Development of Inflammatory Angiogenesis by Local Stimulation of Fas In Vivo. J. Exp. Med. Volume 186, Number 1, July 7, 1997 147-152.

Accordingly, the specification discloses and provides written description for angiogenic agents in both the context of the first and second therapeutic agents.

As amended claims 1 and 26 recite a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent. On page 17, lines 6-9, the specification states that whereas the first therapeutic agent of the invention has a genetic component, the second therapeutic agent can have non-genetic material. Non-genetic material is further defined as any molecule or compound that induces a beneficial biological or medical reaction.

Reading the description of the preferred embodiment reproduced above and Example 7

in the specification, it is instantly clear to one of skill in the art that in the context of this invention "any molecule or compound that induces a beneficial biological or medical reaction" could include an agent that promotes angiogenesis, i.e., an angiogenic agent, as stated on page 18, line 1. Example 7 indicates that examples of angiogenic agents are VEGF and FAS ligand. Therefore, one of ordinary skill in the art would readily appreciate that an exemplary "second therapeutic agent" could be among others, VEGF protein or FAS ligand protein.

The Examiner's statement that there is "nothing in the specification that would lead one to the particular combination set forth in the amended claims" is thereby proven to be without merit. Accordingly, the specification provides adequate written description for claims 1 and 26 as amended on March 17, 2003 and said amendments did not add new matter into the subject application. Withdrawal of this rejection is respectfully requested.

Rejection of claims 17, 30, 37, 50, 52, and 56 under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 17 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The claim has been amended to recite a polymeric coating. Withdrawal of this rejection is respectfully requested.

The Examiner has rejected claim 30 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The Examiner states that there is insufficient antecedent basis for the claim limitation, "said non-plasmid vector". Applicant intended to cancel claim 30 without prejudice in the previous amendment and does so again herewith. Withdrawal of this rejection is respectfully requested.

The Examiner has rejected claim 37 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The claim has been amended to remove the recitation "said carrier". Withdrawal of this rejection is respectfully requested.

The Examiner has rejected claim 50 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The Examiner opines that the term "small molecule" is a relative term and that one of ordinary skill in the art would not reasonably be apprised of the scope of the invention. Applicant respectfully disagrees.

The term "small molecule" is a term of art that refers to compounds synthesized using techniques such as combinatorial chemistry for use as a library from which candidate lead compounds can be isolated for activity in a particular biological assay. Usually, such compounds are potential drugs that work by specifically binding and thereby potentiating, inhibiting or otherwise modulating macromolecule, i.e. DNA, RNA or protein, activity to treat a given disease by addressing its molecular etiology. More information on such molecules can be obtained from

the internet under: http://www.small-molecule-drug-discovery.com/ Accordingly, the skilled artisan would know precisely what is meant by the term of art "small molecule" and as such, withdrawal of this rejection is respectfully requested.

The Examiner has rejected claims 52 and 56 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The Examiner opines that the term "site-specific" is a not defined and that one of ordinary skill in the art would not reasonably be apprised of the scope of the invention. Examiner indicates an erroneous understanding of site specificity as relating to selective replication or targeting within a mammal. Applicant respectfully disagrees.

In the context of vectors, the term "site-specific" is a term of art that refers to the particular locus on an endogenous DNA strand, for example a chromosome, wherein an exogenous DNA, for example vector polynucleotides such as viral DNA or transposable DNA, will integrate. The skilled artisan would appreciate that when utilizing a vector to introduce exogenous DNA into a cell, it is preferable not to have that DNA integrate at a locus such that it might disrupt the normal function of genes vital to the target cell or host organisms' health. Accordingly, it is preferable to use a "site-specific" vector that integrates at genetic loci where normal gene function is not impacted.

For example, it has been reported that an interesting feature of wild-type AAV is its site-specific integration into AAVS1, a defined locus on chromosome 19. This site specific integration is mediated by inverted terminal repeats and *Rep78/68*. It has been shown that AAV vectors mutant for the *rep* gene, lack the ability to integrate site-specifically. See: Satoh et al., Site-Specific Integration of an Adeno-Associated Virus Vector Plasmid Mediated by Regulated Expression of Rep Based on Cre-loxP Recombination. *J Virol.* 2000 November; 74 (22): 10631–10638.

Accordingly, the skilled artisan would know precisely what is meant by the term of art "site-specific" in the context of a vector and as such withdrawal of this rejection is respectfully requested.

Rejection of claims 1, 10, 11, 19, 24, 26, 34, 35, 37, 44, 49, 50, 52, 54, 55, 56, 58, and 59 under 35 U.S.C. § 102(b)

The Examiner rejects claims 1, 10, 11, 19, 24, 26, 34, 35, 37, 44, 49, 50, 52, 54, 55, 56, 58, and 59 under 35 U.S.C. § 102(b), as allegedly being anticipated by Isner U.S. Patent No. 5,652,225. The Examiner alleges that Isner teaches a method for delivery of an angiogenic factor combined with other angiogenic genes or gene products to an arterial cell. Applicants respectfully traverse.

Applicants respectfully assert that among other short comings, Isner does not teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; in combination with a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent.

Applicant respectfully directs the Examiner's attention to Isner, Column 7, ¶1, which states:

> "In certain situations, it may be desirable to use DNA's [sic] encoding two or more different proteins in order [sic] optimize the therapeutic outcome. For example, DNA encoding two angiogenic proteins, e.g., VEGF and bFGF, can be used, and provides an improvement over the use of bFGF alone. **Or an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells**, while simultaneously including angiogenesis, including, for example, nitric oxide synthase, L-argine, [sic] fibronectin, urokinase, plasminogen activator and heparin." (Emphases added)

Accordingly, Isner, describes the possible delivery of: 1) DNAs encoding two or more different angiogenic proteins; 2) an angiogenic factor and other genes, i.e. DNAs **not encoding an angiogenic factor**; or 3) an angiogenic factor and the encoded gene products of other genes, i.e. an angiogenic factor and **a non-angiogenic gene product** [a non-genetic non-angiogenic agent]. Applicant further notes that above-reproduced paragraph provides examples of **such other non-angiogenic gene products**: "nitric oxide synthase, L-argine, [sic] fibronectin, urokinase, plasminogen activator and heparin", none of which are an "angiogenic protein", as defined by Isner, Column 3, lines 40-42. Moreover, none of the aforementioned gene products of other genes, i.e. genes encoding non-angiogenic procucts, are included as examples of an "angiogenic protein" in Isner, Column 3, lines 43-50.

However, the claims at issue recite a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent **is an angiogenic agent**.

As such Isner does not teach every element of the claimed invention. Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejection of claims 1, 17, 19, 20, 26, 42, 44 and 47 under 35 U.S.C. § 103(a)

The Examiner rejects claims 1, 17, 19, 20, 26, 42, 44 and 47 under 35 U.S.C. § 103(a), as allegedly being unpatentably obvious over Isner (U.S. Patent No. 5,652,225) in view of

Donovan et al., (U.S. Patent No. 5,833,651, hereinafter "Donovan").

The Examiner concedes that Isner does not teach specifically making and using a medical device comprising a biocompatible structure carrying a genetic material wherein the structure is a metallic stent. The Examiner opines that this shortcoming is overcome by Donovan which allegedly teaches stents. Applicants respectfully disagree.

As discussed above, Isner does not teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; in combination with a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent. Donovan also fails to teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent encoding an angiogenic agent in combination with a second therapeutic agent comprising a non-genetic angiogenic, as claimed. As such, Donovan's disclosure of metallic stents cannot cure the defects of Isner to render the claimed invention upatentably obvious.

Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejection of claims 1, 3, 24, 25 and 27 under 35 U.S.C. § 103(a)

The Examiner rejects claims 1, 3, 24, 25 and 27 under 35 U.S.C. § 103(a), as allegedly being unpatentably obvious over Isner (U.S. Patent No. 5,652,225) in view of Branellec et al., (U.S. Patent No. 5,851,521, hereinafter "Branellec").

The Examiner concedes that Isner does not teach specifically using an andeno-associated viral (AAV) vector in a medical device or a method of treating restenosis in a site of mechanichal injury to an arterial wall produced by treatment of an atherosclerotic lesion by angioplasty. The Examiner opines that this shortcoming is overcome by Branellec which allegedly teaches use of AAVs a carrying a nucleic acid endcoding GAX protein. Applicants respectfully disagree.

Once again, as illustrated above, Isner does not teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; in combination with a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent. Branellec also fails to teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent encoding an angiogenic agent in combination with a second therapeutic agent comprising a non-genetic angiogenic, as claimed. As such,

Branellec's disclosure AAVs a carrying a nucleic acid endcoding GAX protein does not provide the claimed elements not taught in Isner to render the claimed invention upatentably obvious.

Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejection of claims 1, 18, 26 and 43 under 35 U.S.C. § 103(a)

The Examiner rejects claims 1, 3, 24, 25 and 27 under 35 U.S.C. § 103(a), as allegedly being unpatentably obvious over Isner (U.S. Patent No. 5,652,225) in view of Lennox et al., (US Patent No. 6,280,411, hereinafter "Lennox").

The Examiner concedes that Isner does not teach specifically a medical device wherein the polymer coating is about 1 to about 40 layers having a thickness of about 1 to about 40mm/layer of coating or using the medical device to deliver a nucleic acid and a non-genetic agent to a cell. The Examiner opines that this shortcoming is overcome by Lennox which allegedly teaches medical devices coated with a polymer that is about 1 to 10mm in thickness with multiple layers. Applicants respectfully disagree.

As illustrated above, Isner does not teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; in combination with a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent. Lennox also fails to teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent encoding an angiogenic agent in combination with a second therapeutic agent comprising a non-genetic angiogenic, as claimed. As such, Lennox's disclosure relating to polymer thickness and layer number does not supply the claimed elements not taught in Isner to render the claimed invention upatentably obvious.

Accordingly, Applicant respectfully requests withdrawal of this rejection.

CONCLUSION

It is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Respectfully submitted,
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